Gbx2, a LIF/Stat3 target, promotes reprogramming to and retention of the pluripotent ground state.

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Public Summary:
Signal transducer and activator of transcription 3 (Stat3) is a transcription factor and can be activated by a cytokine called leukemia inhibitory factor (LIF). LIF/Stat3 signaling plays an important role in facilitating reprogramming to the pluripotent embryonic stem cell state and retaining the identity of embryonic stem cells. How LIF/Stat3 exerts these effects, however, is still largely unknown. Here, we found that LIF/Stat3 induces the expression of a gene called gastrulation brain homeobox 2 (Gbx2) and increasing the expression of Gbx2 can mimic the effect of LIF/Stat3 signaling in maintaining embryonic stem cell identity. We also found that elevated Gbx2 expression is sufficient to reprogram epiblast stem cells (a type of pluripotent stem cells derived from the post-implantation epiblast) to embryonic stem cells. Our results reveal a new mechanism on how embryonic stem cell identity is maintained and promoted by LIF/Stat3 signaling and will lead to the development of better culture conditions for the propagation of embryonic stem cells

Scientific Abstract:
Activation of signal transducer and activator of transcription 3 (Stat3) by leukemia inhibitory factor (LIF) maintains mouse embryonic stem cell (mESC) self-renewal and also facilitates reprogramming to ground state pluripotency. Exactly how LIF/Stat3 signaling exerts these effects, however, remains elusive. Here, we identified gastrulation brain homeobox 2 (Gbx2) as a LIF/Stat3 downstream target that when overexpressed allows long-term expansion of undifferentiated mESCs in the absence of LIF/Stat3 signaling. Elevated Gbx2 expression also enhanced reprogramming of mouse embryonic fibroblasts to induced pluripotent stem cells. Moreover, overexpression of Gbx2 was sufficient to reprogram epiblast stem cells (EpiSCs) to ground state ESCs. Our results reveal a novel function of Gbx2 in mESC reprograming and LIF/Stat3-mediated self-renewal.